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ORIGINAL ARTICLE

The Role of Genetic Biomarkers on Post-stroke Cognitive Impairment: A Systematic Review

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ABSTRAK

Kemerosotan kognitif adalah komplikasi yang biasa berlaku selepas strok. Dalam kajian ini, kami bertujuan untuk mengkaij secara sistematik biomarker genetik yang mempengaruhi kemerosotan kognitif selepas strok. Kami menjalankan pencarian secara sistematik dengan menggunakan pangkalan data elektronik (PubMed, PsycINFO, EMBASE, Medline OVID, dan SCOPUS) terhad kepada kajian manusia dari Januari 2011 sehingga 6 Ogos 2021 dengan menggunakan istilah-istilah pencarian yang berkaitan. Kajian ini dijalankan mengikut Garis Panduan Pelaporan Keutamaan untuk Kajian Sistematik dan Meta-Analisis (PRSIMA). Daripada 6,523 rujukan yang diimport, hanya 9 kajian yang dimasukkan untuk sintesis akhir. Kajian ini menunjukkan bahawa biomarker keradangan seperti alel 'brain-derived neurotrophic factor' (BDNF) Val66Met dan alel G196A, Interleukin-12 (IL-12), 'rheumatoid factor' (RF), 'vascular endothelial growth factor' (VEGF), Apoprotein E (ApoE) e4, dan high sensitivity Cardiac Troponin T (hs-cTnT) mempunyai kaitan dengan kemerosatan kognitif pada pesakit strok. Sementara itu, ApoE2 dan alel risiko polimorfisme nukleotida tunggal rs3744028 di lokus Chr17q25 adalah gen pelindung terhadap kemerosotan kognitif selepas strok. ApoE3 wujud pada semua pesakit pasca strok. Kajian ini terhad kepada manusia dan artikel-artikel yang diterbitkan sahaja yang dimasukkan. Proses untuk mengkaji pengaruh genetik terhadap hasil kognitif selepas strok, banyak dijalankan secara meluas pada binatang, mengambil masa dan kos yang tinggi. Dengan demikian ianya menyumbang kepada sampel yang kecil untuk sintesis akhir serta

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heterogeniti dalam kajian. Kajian ini menunjukkan bahawa biomarker keradangan, kardiovaskular, dan ApoE memainkan peranan penting dalam meramalkan fungsi kognitif selepas strok. Memahami mekanisme molekul hasil kognitif selepas strok dapat membimbing penyelidik dan pakar klinikal dalam membangunkan rawatan yang tepat dan rawatan individu untuk strok pada masa akan datang.

Kata kunci: Biomarker; kemerosotan kognitif selepas strok; kemerosotan kognitif

ABSTRACT

Cognitive deficit has been an established complication following stroke. In this study, we aimed to systematically review genetic biomarkers that influenced cognitive deficit following stroke. We systematically searched using multiple electronic databases, limited to human studies from January 2011 until August 6, 2021 using search-related terms. The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). Out of the 6523 references were imported, 9 studies were included for final synthesis. This study revealed that inflammatory biomarkers such *as brain-derived neurotrophic factor (BDNF) Val66Met* allele and *G196A* allele*, Interleukin-12 (IL-12), Rheumatoid Factor (RF), vascular endothelial growth factor (VEGF), Apoprotein E (ApoE) e4*, and *high sensitivity Cardiac Troponin T (hs-cTnT)*, were associated with cognitive impairment in stroke patients. Meanwhile, *ApoE2* and the risk allele of single nucleotide polymorphism (SNP) *rs3744028* in *Chr17q25* locus were protective genes against post-stroke cognitive impairment. *ApoE3* presented in all post-stroke patients. This review showed that inflammatory, cardiac, and *ApoE* biomarkers play an important role in predicting cognitive function post-stroke. Understanding the molecular mechanisms of cognitive outcome following a stroke can guide researchers and clinicians in developing future precision and personalised treatment for stroke.

Keywords: Biomarkers; cognitive impairment; post-stroke cognitive impairment

INTRODUCTION

Stroke remains as the second-leading cause of death and one of the leading causes of chronic debilitating disease in the world (Feigin et al. 2022). Annually, approximately 15 million people suffer a stroke across the globe, and out of these figures, 5 million passed away while another 5 million suffered permanent disabilities (WHO Eastern Mediterranean Region 2022). Over the past 3 decades, the disability-adjusted life years showed a staggering increase by at least 32 per cent, more prominently in the lower-income and lower-middle-income countries (LMIC) (GBC 2019 Stroke Collaborators 2021).

These figures are corroborated by the estimated global cost of stroke, which is currently estimated to be around US$ 721 billion, amounting to 0.66% of the global gross domestic product (GDP).

Risk factors of stroke associated cognitive impairment are multifactorial, including demographic factors, such as, older age, hereditary, genetic variants, low educational status; cardiovascular factors (hypertension, heart disease, atrial fibrillation); metabolic factors (artherosclerosis, obesity, diabetes mellitus, dyslipidemia); lifestyle factors (physical inactivity, cigarette smoking, alcoholism, substance abuse); as well as other vascular comorbidities, such as hypercoagulopathy, endothelial dysfunction, hemostatic abnormalities (Kaur & Sharma 2022).

Post-stroke cognitive impairment (PSCI) is one of the major morbidity after stroke worldwide (Rost et al. 2022). This cognitive impairment could occur after either ischaemic or vascular stroke and could lead to vascular dementia. Few studies have suggested that the prevalence of cognitive impairment in stroke survivors is estimated between 70 to 90% (Jaillard et al. 2009; Jokinen et al. 2015; Stolwyk et al. 2021). With that worrying figure, it is often forgotten that the cognitive decline significantly impacts not just the patient alone, but extends to the family members and carers as well, which requires huge resources to care for the patient, as well as affects their physical and mental health (Hu et al. 2018).

Hence, researchers and clinicians over the past decade have adopted a paradigm shift, focusing on proactive management of stroke and its complications. As we are heading towards precision medicine, one promising avenue in stroke research that has shown growing interest is the genetic biomarkers. Studies have suggested the possible role of biomarkers to predict cognitive decline in at least one of the cognitive domains after an episode of stroke. A systematic review and meta-analysis on potential peripheral biomarker for PSCI by Kim et al. in 2022 found that homocysteine (Hcy), C-reactive Protein (CRP), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were noted to be significantly higher compared to those without PSCI. Another review by Zhang and Bi in 2020 also highlighted the correlation between an increase in the biomarkers CRP, interleukin-6 (IL-6), and IL-10 in blood, urine and other body fluids with patients with PSCI. However, to our knowledge, no previous systematic study has been done to specifically examine the link between genetic biomarkers with PSCI. Therefore, this study aimed to systematically examine studies related to genetic biomarkers that influence PSCI.

MATERIALS AND METHODS

This review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and was registered in International prospective register of systematic reviews PROSPERO (CRD42021260902).

Search Strategy and Study Identification/Selection

Systematic search was performed using electronic databases PubMed, PsycINFO, EMBASE, Medline OVID and SCOPUS, limited to English language and human study. Articles selected from January 2011 and the last search was carried out on August 6, 2021. The following search terms were used: [('post-stroke' OR 'stroke' OR 'cerebrovascular accident' OR 'transient ischaemic attack' OR 'mini stroke' OR 'cerebral vascular insult' OR 'brain attack') AND ('cognitive impairment' OR 'cognitive deficit' OR 'dementia') AND (gene*)] (MeSH term).

Titles and abstract of all publications were screened by two authors (DCW and TWH) independently, using COVIDENCE software, to select studies for full text review. During all stages, in the case of disagreement, consensus was reached through discussion with a third author (SMS). The full texts of the articles were then reviewed to determine whether they would be included by the authors.

Studies were eligible for inclusion if they examined genetic biomarkers in post-stroke patients (either ischaemic or haemorrhagic stroke) with cognitive impairment. No restrictions were placed on sample size or method of data collection. We excluded reviews, case-report, meeting/conference abstracts, non-genetic biomarkers study, and animal study.

Data Extraction

For all eligible studies, the following data were extracted using a standardised collection sheet: genetic biomarkers, country of study, study design (cohort, case-control, or cross-sectional), number of patients (with stroke/without stroke), cognitive domain and overall finding.

Quality Assessment

The study quality assessment tools of the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) for quality assessment of Case-Control Studies and quality assessment tool for Observational Cohort and Cross-Sectional Studies were used to assess the quality of included studies (National Heart, Lung and Blood Institute).

RESULTS

As shown in Figure 1, in total, 8,888 articles (PubMed = 2824, PsycINFO = 454, EMBASE = 3375, Medline OVID = 1004, and SCOPUS = 1231) were identified through database searching. After removing duplicates, 6523 articles were screened. Subsequently, the full-text articles of 59 records were assessed for eligibility, of which 50 were excluded. Lastly, 9 studies were selected for analysis.

The characteristics of the included studies were highlighted in Table 1 (Broersen et al. 2020; Donnellan et al. 2019; Han et al. 2020; Keshavarz et al. 2016; Narasimhalu et al. 2015; Prodjohardjono et al. 2020; Rezaei et al. 2020; Tabara et al. 2013; Zhu et al. 2019). The 9 studies reviewed included 3434 participants in total,

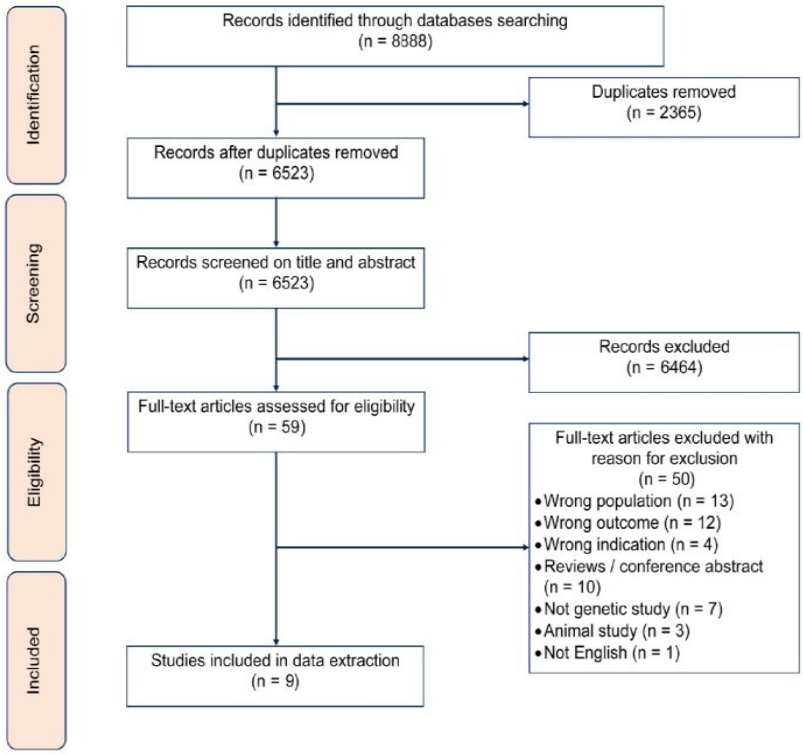

FIGURE 1: PRISMA flow chart outlaying the selection procedure to identify 9 studies included in the systematic review of genetic biomarkers for cognitive impairments in post-stroke patients

including 3180 stroke patients, 253 normal healthy controls. Study designs included 2 case control, 4 cohort, and 3 cross-sectional.

The genetic biomarkers most frequently studied were brain-derived neurotrophic factor (BDNF), and each on Apoprotein E (ApoE), Interleukin-12 (IL-12), vascular endothelial growth factor (VEGF), Rheumatoid Factor (RF), high sensitivity Cardiac Troponin T (hs-cTnT) and Chr17q25. The genetic biomarkers with the greatest number of patients studied were Chr17q25 (1190 patients), followed by hs-cTnT (555 patients), BDNF (498 patients), IL-12 (243 patients) and other biomarkers (ApoE and VEGF) accounting for less than 100 patients per biomarker.

The majority of the studies used Montreal Cognitive Assessment (MOCA) and Mini Mental State Examination (MMSE) as a measurement tools to evaluate cognitive function. Other tools used were Addenbrooke's Cognitive Examination Third Edition (ACE-III), Touch Panel type Dementia Assessment Scale (TDAS), Telephone Interview for Cognitive Status-modified (TICS-m), functional independence measures and non-memory & memory domain for each study.

TABLE 1: Studies characteristic and finding

Authors, year	Biomarkers	Country	Study design	Duration	Number of cases/ control	Cognitive domain	Overall findings
Broersen et al. 2020	hs-cTnT	German	Cohort	3 years	555 (ischaemic stroke)	MMSE; TICS-m	Higher hs-cTnT was associated with worse cognitive function at baseline and during 3-year follow-up.
Donnellan et al. 2019	Apoprotein E e2 e3 e4	Bahrain	Case-control	Within 1 - 2 weeks post-stroke	62 (ischaemic stroke) / 53 (healthy)	MMSE; MOCA	The stroke patient with ApoE2 positive performed better in global cognition. In the control group, participants with ApoE3 scored better. The stroke patients performed better on all cognitive measures where ApoE4 was absent.
Han et al. 2020	BDNF (Val66Met)	US	Case only	Until patient discharge from the ward (usually above 6 days).	86 (34 ischemic and 52 haemorhagic)	Functional Independence Measures	Patients with a Met alleles genotypes had a significant correlation with lower cognitive scores [p = 0.005; OR = 2.30 (0.73-3.87)] and [p = .004; OR = 2.77 (0.93-4.61)], and less cognitive recovery [p = 0.046; OR = 2.40 (0.04-4.75)] and [p = 0.049; OR = 2.39 (0.10-4.77)], for both ischaemic and haemorhagic stroke respectively.
Keshavarz et al. 2016	BDNF (G196A)	Iran	Case-control	6 months	206 (ischaemic stroke) / 200	MOCA – cognitive domain	GA+GG (G allele carrier) were more susceptible of cognitive impairment after ischaemic stroke (p = 0.002) compared to AA homozygotes carrier after 6 months of ischaemic stroke.
Narasimhalu et al. 2013	IL-12	Singapore	Cohort	6 years	243 (ischaemic stroke)	Nonmemory & memory domain*	IL-12 (OR = 25.02; p 0.05; CI: 3.73-168.03) was an independent predictor of cognitive decline.
Prodjohardjono et al. 2020	VEGF	Indonesia	Cohort	3 months	56 (ischaemic stroke)	MOCA -Indonesian version	Higher VEGF level (519.8pg/ml) alone (after controlling all variables) was more likely to have PSCI than those with lower VEGF level (OR = 4.99, 95% CI = 1.01–24.7, p = 0.048).

Rezaei et al., 2020	BDNF (Val66Met)	Iran	Case only	2 years	206 (ischaemic stroke)	ACE-III	Carriers of at least one Val allele had more cognitive deficits than Met/Met homozygotes.
Tabara et al. 2012	Chr17q25 (rs3744028)	Japan	Cross-sectional	-	1190	TDAS	The risk allele of SNP rs3744028 was protective for mild cognitive impairment independent of WMH grade (p = 0.04).
Zhu et al. 2019	RF	China	Case only	3 months	582 (ischaemic stroke)	MMSE; MOCA	The highest tertile of serum RF (7.61 IU/ml) was associated with risk of cognitive impairment [p = 0.03; OR = 1.79 (1.08 – 2.99)] and [p = 0.01; OR 2.08 (1.20 – 3.60)] at 3 months post-stroke, based on MMSE and MOCA respectively.

Methodological Quality

The result for methodological quality was shown in Supplementary Table 1 and 2. This study revealed that BDNF polymorphism, VEGF, ApoE4, IL-12, RF and cardiac Troponin T were associated with cognitive impairment in stroke patients. Whereas, ApoE2 and those who had risk allele of SNP rs3744028 in Chr17q25 locus were protective factors against post-stroke cognitive impairment and mild cognitive impairment. ApoE3 presented in all post-stroke patients.

DISCUSSION

To the best of our knowledge, this is the first systematic review on genetic biomarkers of post-stroke cognitive impairment. In this review, we aimed to identify genetic biomarkers that influence cognitive impairment following stroke. A total of 9 papers were identified. Our findings show that inflammatory, cardiac and *ApoE* biomarkers do predict cognitive dysfunction post-stroke. Based on these findings, we demonstrate possible pathways that can lead to cognitive impairment following stroke, in relation to genetic biomarkers in Figure 2.

Cerebral hypoperfusion could occur following a stroke, which leads to neuronal damage and cell death. It is fundamental for the brain to restore blood flow as soon as possible in response towards neuronal damage and death via activation of neurogenesis and angiogenesis pathway, and removing the cell

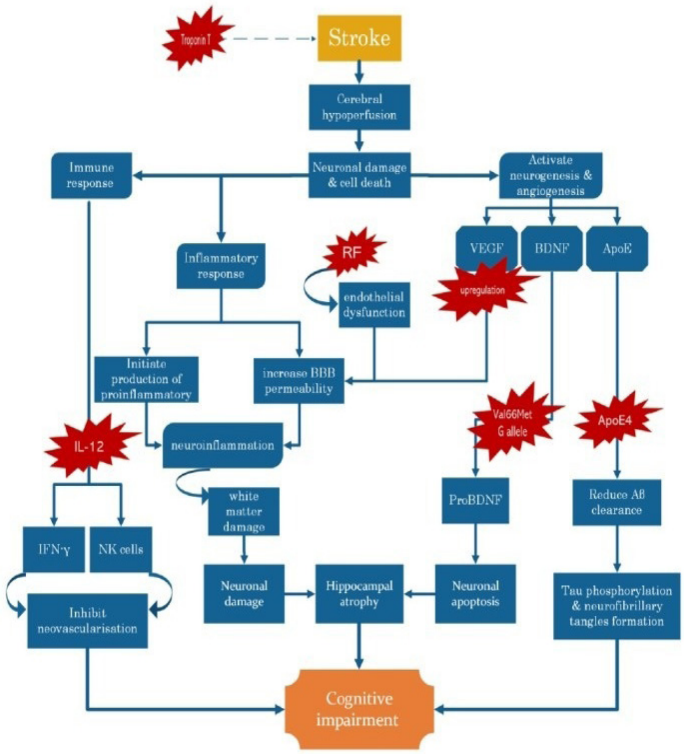

FIGURE 2: pathway of cognitive impairment following stroke, in relation to genetic biomarkers

death via inflammatory and immune responses.

Reperfusion activates the inflammatory and immune responses. The cascade of inflammatory and immune responses will lead to increase neuroinflammation via initiating the production of proinflammatory as well as increasing the blood-brain barrier (BBB) permeability (Gelderblom et al. 2009) due to endothelial dysfunction (Cipollini et al. 2019). Microglial cells are the first cell that will be activated and increased dramatically (Purves 2001). Followed by the infiltration of macrophages, dendritic cells, lymphocytes and neutrophil (Cipollini et al. 2019; Gelderblom et al. 2009) to the damaged cells and participate in clearing the dead cells and cellular debris (Doyle & Buckwalter 2017; Purves et al. 2001). The increased BBB permeability also contributes to the infiltration of inflammatory factors like interleukins, chemokines, cytokines, matrix metalloproteinases (MMPs), tumor necrosis factor-α (TNF-α), toll-like receptor 4 (TLR4), CRP (Cipollini et al. 2019).

The release of protease and exposure of neural cells to inflammatory environment will lead to white matter damage, subsequently causing neuronal damage (Cipollini et al. 2019; Enzmann et al. 2018; Pan et al. 2007) and further hippocampal atrophy.

This is true in the reperfusion injury concept whereby following stroke, numerous mechanisms happened ranging from release of excitatory amino acids and ion-dysequilibrium to apoptosis and necrosis, to oxidative stress and inflammation (Enzmann et al. 2018), as well as activation of autoimmunity (Doyle & Buckwalter 2017), which finally contributing to neurodegeneration and cognitive impairment (Doyle & Buckwalter 2017).

Interleukin 12 (IL-12), is a multifunctional cytokine produced by macrophages and B-cell lines. IL-12 will activate interferon-gamma (IFN-γ) production and stimulate Natural Killer (NK) cells, which then inhibit neovascularisation (Sgadari et al. 1996). Brain structure required vascularisation, for viability through oxygenation. However, when there was lack of neovascularisation, the cerebral will further damage. The long-term inhibition of neovascularisation can be the possible mechanism which leads to cognitive impairment as the neuron is unable to repair adequately after stroke.

Narasimhalu et al. (2015) studied on the association between inflammatory markers and post-stroke cognitive decline. The inflammatory markers include C-reactive protein, Interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-12 and TNF-α. However, only IL-12 resulted as a strong predictor of cognitive decline over the years.

IL-12 plays a role in cognitive decline in stroke patients in addition to its role in the immune response. The inhibition of long-term neo-vascularisation after a stroke may be a possible explanatory mechanism for the propensity of stroke patients with higher levels of IL-12 to deteriorate cognitively (Narasimhalu et al. 2015).

Rheumatoid Factor (RF)

Another interesting study that we found which can be a promising predictor for post-stroke cognitive function is RF. The study found that post-stroke patients who had a higher level of serum RF were associated with a higher risk of cognitive impairment (Zhu et al. 2019). It can be explained by the direct effect of RF on the endothelium. RF is an autoantibody that targets the Fc fragment of IgG (Vincent et al. 2011) forming immune complexes (Kato et al. 2000). These immune complexes had a direct effect on endothelium (Kato et al. 2000). Endothelial dysfunction via the *RF* complex could further increase BBB permeability, thus exposing the neural cells to harmful substances (Cipollini et al. 2019; Vincent et al. 2011). This will result in neuroinflammation and neural damage, which lead to cognitive impairment (Cipollini et al. 2019; Doyle & Buckwalter 2017).

Vascular Endothelial Growth Factor (VEGF)

Study by Prodjohardjono et al. (2020) on serum VEGF levels in post-stroke cognitive impairment, found that upregulation of VEGF may bring down the cascade of increasing the BBB and thus leading to neuroinflammation. The possibility of higher VEGF levels

is due to a more robust and severe process of hypoxia or ischaemia in patients with severe stroke, leading to cognitive impairment due to a chronic hypoperfusion state.

VEGF is known for its impact on neuroprotective and angiogenic effects as well as in the regulation of vascularisation (Góra-Kupilas & Jośko 2005; Ma et al. 2012; Namiecińska et al. 2005). Contradictory, upregulation levels of VEGF are detrimental in acute stroke, due to VEGF-mediated blood-brain-barrier breakdown and vascular leakage, leading to oedema and neuroinflammation (Geiseler & Morland 2018).

Brain-derived Neurotrophic Factor (BDNF)

BDNF is synthesised as a precursor protein (proBDNF) and transformed into its mature form either intra or extracellularly by undergoing proteolytic cleavage (Borodinova & Salozhin 2016; Lessmann et al. 2003). BDNF and proBDNF have opposing effects on cellular function (Miranda et al. 2019). Mature BDNF plays an important role in the regulation of synaptic plasticity and neuronal regeneration, related to learning and memory (Chen et al. 2004; Lu et al. 2005; Miranda et al. 2019), whereas proBDNF promotes apoptosis (Chen et al. 2004) leading to hippocampal atrophy.

Polymorphism in BDNF (Han et al. 2020; Keshavarz et al. 2016; Rezaei et al. 2020) gene at single nucleotide 196, transform from guanine (G) to adenosine (A), thus altering the amino acid production from valine to methionine protein at codon 66 (Egan et al. 2003). These mutations in the G allele reduced proBDNF to transform into mature BDNF form (Chen et al. 2004; Egan et al. 2003), thus leading to an imbalance in proBDNF and BDNF production. Therefore, the balance of concentrations of proBDNF and mature BDNF is important in nerve cell survival (Borodinova & Salozhin 2016; Chen et al. 2004; Egan et al. 2003).

Apoprotein (Apo) E

ApoE has 3 major isoforms – ApoE2, ApoE3 and ApoE4, with ApoE3 being the most common. Its major function is to mediate the binding of lipoprotein or lipid complexes in the plasma (Huang & Mahley 2014) and has roles in modulating amyloid beta (Aβ) metabolism, aggregation and deposition (Castellano et al. 2011).

We found that ApoE4 had greater impairment in cognition, which is consistent with other studies (Donnellan et al. 2019; Farlow et al. 2004; Williams et al. 2020). On the other hand, ApoE2 is a protective factor against cognitive impairment (Donnellan et al. 2019; Pedersen et al. 2000; Williams et al. 2020).

ApoE4 decreases Aβ clearance and increases amyloid fibril formation (Huang & Mahley 2014) as well as causes cytoskeletal structure changes (Huang & Mahley 2014; Machulda et al. 2011), stimulates tau phosphorylation (Huang & Mahley 2014; Williams et al. 2020) that leads to neurofibrillary tangles formation, inhibits neurite

outgrowth (Huang & Mahley 2014) and impaired neuronal plasticity (Huang & Mahley 2014) leading to hippocampal atrophy (Huang & Mahley 2014) and neurodegeneration and cognitive impairment (Farlow et al. 2004; Huang & Mahley 2014).

Cardiac Troponin T (hs-cTnT)

Indirect finding that we found from our review was a cohort study by Broersen et al. (2020). He revealed that ischaemic stroke patient who had higher hs-cTnT was associated with worse cognitive function at baseline. However, there was no difference in the rate of change of a cognitive function over time.

Possible underlying mechanisms that may contribute to cognitive dysfunction include shared vascular risk factors which lead to damage to both organs simultaneously (Berry et al. 2019; Broersen et al. 2020; Schneider et al. 2014). Another potential mechanism is stroke-associated cardiac alteration also called a stroke-heart syndrome. Following a stroke, there will be a possibility of alteration in the central autonomic network function and structure which subsequently lead to dysregulation of normal neural cardiac control. This dysregulation can damage the myocardium, thus releasing cardiac troponin T (Scheitz et al. 2018). Finally, heart disease may lead to stroke via embolism (Folsom et al. 2013; Yaghi et al. 2018).

There are a few limitations in this study. First, we limit our study to human study. As for the genetic study, it was widely done in animals. There is a lack of direct studies involving humans.Second, to study cognitive outcomes following stroke, requires the study to be done prospectively, which is expensive and time-consuming from a clinical perspective. The processes such as immunosenescence and chronic inflammation have a progressive and time-dependent nature. Another limitation of the study is the heterogeneity of studies, in terms of methodology, such as the timing of cognitive assessment following the stroke event, duration of the study, study design and cognitive measures. Hence, we are unable to proceed with meta-analysis due to the heterogeneity of the studies and the variation of reported effect sizes.

CONCLUSION

In conclusion, we found that BDNF polymorphism, VEGF, ApoE4, IL-12, RF and cardiac Troponin T were associated with cognitive impairment in stroke patients. However, ApoE2 and SNP rs3744028 in the Chr17q25 locus were protective factors against post-stroke cognitive impairment and mild cognitive impairment. The balance between activation of VEGF, BDNF and production of ApoE are important determinants of the viability of neurons and subsequently predict cognitive outcomes following stroke. Understanding the pathophysiology and molecular mechanisms of cognitive outcomes following stroke can guide researchers and clinicians in developing future precision and personalised treatment for stroke.

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